Prevalence, pathogenesis and spectrum of neurological symptoms in COVID-19 and post-COVID-19 syndrome: a narrative review

Robb Wesselingh[1,2]

Summary

- Neurological symptoms are not uncommon during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and reflect a broad spectrum of neurological disorders of which clinicians should be aware.
- The underlying pathogenesis of neurological disease in coronavirus disease 2019 (COVID-19) may be due to four mechanisms of nervous system dysfunction and injury: i) direct viral neurological invasion; ii) immune dysregulation; iii) endothelial dysfunction and coagulopathy; and iv) severe systemic COVID-19 disease.
- Neurological manifestations of acute COVID-19 include headache, peripheral neuropathies, seizures, encephalitis, Guillain–Barré syndrome, and cerebrovascular disease.
- Commonly reported long term neurological sequelae of COVID-19 are cognitive dysfunction and dysautonomia, which despite being associated with severe acute disease are also seen in people with mild disease.
- Assessment of cognitive dysfunction after COVID-19 is confounded by a high prevalence of comorbid fatigue, anxiety, and mood disorders. However, other markers of neuroaxonal breakdown suggest no significant neuronal injury apart from during severe acute COVID-19.
- The long term impact of COVID-19 on neurological diseases remains uncertain and requires ongoing vigilance.

Since the initial report from Wuhan, China, of neurological symptoms occurring in 36.4% of patients with coronavirus disease 2019 (COVID-19),[1] there have been efforts across the globe to identify the potential neurological manifestations of the disease. These efforts have ranged from global registries to multicentre and single centre case series, and were vital to improve our understanding of what clinicians may expect to see as COVID-19 spread. Although case definitions of the various neurological symptoms and syndromes have been fairly uniform internationally, there is a great deal of heterogeneity with regards to case ascertainment. The chaotic nature of the COVID-19 pandemic meant that patient recruitment was often opportunistic, with great differences between variables such as patient location and COVID-19 severity. This is reflected in the wide variance in the reported prevalence of both neurological presentations in COVID-19, ranging from 7% to 77.8%, and the breakdown of the type of neurological complaints (Supporting Information). For example, the prevalence of headache has been reported to be as high as 41.1%[2] or as low as 4.3%.[3]

Registries worldwide are beginning to provide an overview of the spectrum of neurological manifestations of COVID-19. A meta-analysis has collated the multiple registry and case series of neurological symptoms of COVID-19 to provide a point prevalence for each of the most common symptoms.[4] Overall, anosmia, dysgeusia and headache are common symptoms. Encephalopathy, encephalitis, cerebrovascular disorders, and peripheral neuropathies, including Guillain–Barré syndrome (GBS), are all described in COVID-19 but are less common. Seizures and movement disorders appear to be rare.

This narrative review will explore the characteristics of the neurological diseases seen during acute COVID-19, the evidence for long term neurological complications, and summarise the potential pathological mechanisms involved. Relevant literature was identified by searching PubMed, Google Scholar and MEDLINE for articles published from 2019 to 2022 with the search terms "COVID" and "neurology".

Pathophysiological mechanisms of neurological disorders in COVID-19

The underlying pathogenesis of neurological symptoms in COVID-19 is heterogenous and multifactorial. Of these, there are four likely mechanisms of nervous system dysfunction and injury that occur during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: i) direct neurological invasion and injury by the virus; ii) para-infectious autoimmune responses directed against the nervous system; iii) endothelial dysfunction and COVID-19-associated coagulopathy; and iv) toxic effects of severe systemic COVID-19 disease on the neuroaxis. These mechanisms are not mutually exclusive and, in many cases, occur concurrently. However, for simplicity, this discussion will be focused on the primary mechanism present in each of the clinical syndromes.

First, neurological manifestations of COVID-19 may occur due to viral neurological invasion. The highly prevalent clinical symptoms of anosmia and dysgeusia, suggesting olfactory bulb and nerve involvement in the setting of high viral loads within the nasopharynx,[5] have raised the possibility of direct viral central nervous system (CNS) invasion. Although there are plausible entry points to the CNS, evidence of neurotropism in animal models and pathological evidence of virus within the CNS, the direct effect of the virus on the CNS remains unknown.[6]

SARS-CoV-2 infects human cells by binding with angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. The main cell type expressing ACE2 receptors in the CNS are neurons, with the olfactory bulb and the choroid plexus showing the highest expression on transcriptomic analysis,[7] which makes these sites the most likely portals of entry into the CNS. Mouse models of SARS-CoV-2 infection have demonstrated viral invasion into the brain via the olfactory nerve.[6] However, as SARS-CoV-2 does not bind well to mouse ACE2 receptors, these models use transgenic mice expressing human ACE2 receptors, which results in an artificial environment. In addition, ACE2 receptors in mice are more highly expressed in the olfactory bulb than that seen in humans.[7] These factors mean that it is difficult to extrapolate these studies to humans and, thus far, these putative mechanisms have not been confirmed *in vivo* in humans.

[1]Monash University, Melbourne, VIC. [2]Alfred Hospital, Melbourne, VIC. robb.wesselingh1@monash.edu • doi: 10.5694/mja2.52063

Pathological studies in humans examining the presence of virus in the CNS have had varied results. A study published in 2021 examined the post mortem brain tissue of two patients with anosmia and dysgeusia due to COVID-19 who died of respiratory failure.[8] They identified neuronal injury predominately in the medulla oblongata. Similarly, in a larger case series of 43 autopsies of patients with COVID-19, 37 patients demonstrated astrogliosis and microglial activation, with T cell infiltration being most prominent in the brainstem.[9] The olfactory bulb also showed high degree of astrogliosis and microgliosis. SARS-CoV-2 RNA was identified in the brain parenchyma of 13 of these patients. In both studies, spike protein or nucleocapsid protein immunostaining was prominently seen in neurons and in glial cells in the medulla and lower cranial nerves, particularly the vagus nerve.[8,9] These studies suggest possible viral invasion into the CNS via the vagus nerve. This is anatomically plausible, given the vagus nerve innervates organs such as the lungs and gastrointestinal tract, which are common sites of SARS-CoV-2 infection.

Other studies have either not identified any evidence of virus in the CNS[10,11] or identified viral RNA in the olfactory bulb only.[12] Most of these studies have identified concomitant astrogliosis and microglial activation,[8,9] indicating CNS injury independent of virus and are potentially better explained by other pathogenic mechanisms. Given these findings, it is likely that primary invasion of the CNS by SARS-CoV-2 is rare, and that the uncommon occurrence of virus identified in the CNS is representative of virus movement across a disrupted blood–brain barrier in the setting of a pro-inflammatory environment.

Second, neurological manifestations of COVID-19 may occur due to immune dysregulation. Immune-mediated disease is not unique to COVID-19 and is observed in the setting of several pathogens.[13] This has been postulated to occur either due to loss of self-tolerance of the adaptive immune system activated by a virus, molecular mimicry from similarities between pathogenic- and self-antigens, or as the collateral of an antiviral inflammatory response.[13]

Third, neurological manifestations of COVID-19 may occur due to vascular injury. Disruption of normal coagulation has been well characterised in COVID-19, and thrombotic complications in multiple organs are commonly seen in severe COVID-19.[14] Elevated D-dimer (a marker of microangiopathic changes) is also used as a key biomarker of poor prognosis.[15] Endothelial dysfunction has been identified pathologically in the CNS of patients with COVID-19. This manifests as endotheliitis, which is identified by microbleeds, petechial haemorrhages within the walls of blood vessels, and perivascular infiltration of T cells and macrophages.[16] Endotheliitis has been described in the pons, the thalami, juxta-cortically, and in the deep white matter in large autopsy studies.[16,17]

Finally, neurological manifestations of COVID-19 may occur due to systemic COVID-19 disease. Severe disease in COVID-19 results in hypoxia and a pro-inflammatory state or "cytokine storm", similar to that seen in severe sepsis.[18] Post mortem examination of the brain tissue of patients who died of severe COVID-19 demonstrates widespread inflammation with microglial activation. In these same specimens, there was no evidence of concomitant endotheliitis or evidence of viral invasion,[11,12] indicating these changes are independent of endothelial dysfunction or direct viral injury. Both hypoxia and the inflammatory mediators can cause this potential CNS injury, although these changes are not unique to COVID-19. The same pathological CNS changes were also observed in a second cohort consisting of patients who died of sepsis but were not seen in a non-septic cohort.[12]

Inflammation-related disorders in COVID-19

Headache

Headache is a common early symptom in COVID-19. One cross-sectional study reported headache as the first symptom in 26% of patients.[19] The most common type of headache reported in COVID-19 is bifrontal or holocephalic with a pressure quality and daily in frequency.[20,21] Several studies have identified common associated migraineous symptoms, including photophobia, phonophobia, and gastrointestinal upset.[22] Risk factors identified include female sex, younger age, presence of fever, and dehydration.

Most cases of COVID-19-related headache last about three days, and the majority last no more than two weeks. A follow-up study evaluating patients with headaches during SARS-CoV-2 infection nine months after their illness found that only 19% of patients were still experiencing headaches at the nine-month follow-up.[23] Of the patients who had headache at one month after illness, 50% still had headache at the nine-month time point, suggesting chronicity is established early on.

The aetiology of headache in COVID-19 remains disputed and is likely to be multifactorial. Calcitonin gene-related peptide (CGRP) is a neuropeptide known to play a role in the pathogenesis of migraine and the target of many novel migraine treatments. CGRP receptors are found on the trigeminal ganglion and coexist with ACE2 receptors, indicating a potential target for viral invasion. CGRP levels are also known to increase with inflammatory cytokines such as interleukin (IL)-6, which are also thought to be able to activate local nociceptive sensory neurons and cause nerve inflammation and potentially central sensitisation. Molecular studies in COVID-19-related headache have also been heterogenous. Some studies have demonstrated lower systemic inflammatory markers, such as erythrocyte sedimentation rate, blood leucocytes and serum ferritin,[24] with an increase in the anti-inflammatory cytokine IL-10.[25] Other studies have identified higher serum IL-6, a pro-inflammatory cytokine.[26,27] However, in these studies, patients with headaches also appeared to have more severe pulmonary COVID-19 disease. A better understanding of headache in COVID-19 may translate into a deeper appreciation of the pathogenesis of other headache disorders. Further studies evaluating molecules in the cerebrospinal fluid of patients with COVID-19-related headache would be a valuable addition to this pursuit (Box).

Peripheral nervous system

Peripheral nervous system involvement in COVID-19 (excluding GBS, which will be discussed separately) appears to fall into two main categories: i) rare inflammatory events that have been reported in case reports or case series; and ii) critical illness neuropathy or myopathy due to prolonged severe pulmonary illness. The first category has included events such as brachial plexiitis[28] and steroid responsive diffuse anterior horn cell disease.[29] These disorders are likely to relate to a systemic inflammatory response in the setting of COVID-19, and their treatment is likely to include immunotherapy such as corticosteroids.

The second category is the result of the severe illness that can occur with COVID-19 requiring prolonged inpatient care

Key points on neurological manifestations of coronavirus disease 2019 (COVID-19)

	Key points
Headache in COVID-19	• Headache is common during SARS-CoV-2 infection but usually self-limiting • Patients with ongoing headache after several months are at significant risk of chronic headache • Given the potential involvement of CGRP in the pathogenesis of headache in COVID-19, the use of CGRP-antagonists may be effective to treat chronic headaches in these patients, but further targeted research is needed in this area
Peripheral nervous system	• Inflammatory peripheral nerve syndromes in COVID-19 are uncommon but should be treated initially with corticosteroids, with consideration of further immunotherapy • Critical illness myopathy may play a critical role in the outcome of patients with severe COVID-19, and strategies to limit myopathy should be considered in this population (early physiotherapy, judicious use of corticosteroids and other myotoxic agents) • Autonomic dysfunction in post-COVID-19 syndrome and its relationship to other central sensitisation syndromes require more research; in particular, to evaluate if they benefit from the same management strategies used in such syndromes
Seizures	• Seizures are uncommon *de novo* in COVID-19, so, when present, evaluation for intracranial pathology should be undertaken • SARS-CoV-2 infection may temporarily exacerbate existing seizure disorders • Long term antiseizure therapy is rarely needed
Guillain–Barré syndrome	• The relationship between SARS-CoV-2 infection and Guillain–Barré syndrome remains unclear • Ongoing epidemiological studies are required to continue to evaluate this relationship
Stroke and other cerebrovascular disorders	• Severe SARS-CoV-2 infection is a risk factor for stroke, and clinicians should have a low threshold for stroke evaluation in patients with COVID-19 admitted to hospital who develop new neurological deficits • Whether COVID-19 increases stroke risk in younger patients or in those with mild disease remains unclear, but given the high potential for morbidity, this requires ongoing public health surveillance • COVID-19 can be considered a unique risk factor for venous thrombosis, including central venous sinus thrombosis
Neurological symptoms of the post-COVID-19 syndrome	• Cognition dysfunction after SARS-CoV-2 infection appears to largely relate to disease severity and multiple factors that occur in this setting (hypoxaemia, systemic inflammation, use of anaesthetic agents) • There is a substantial proportion of patients with post-COVID-19 syndrome who present with subjective cognitive complaints that require rigorous ongoing longitudinal evaluation given the potential socio-economic implications of a theoretical COVID-19-associated neurodegenerative syndrome

CGRP = calcitonin gene-related peptide; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. ◆

and, potentially, ventilation. Cohorts of critically ill patients with COVID-19 have identified both electrophysiological and histopathological evidence of critical illness myopathies[30] as well as fairly symmetrical sensory-motor axonal neuropathies.[31] The degree of muscle injury may also play a part in patient outcome. One study identified that muscle injury in COVID-19 was not necessarily associated with a creatinine kinase rise, but that a significant creatinine kinase rise was associated with respiratory failure and in-hospital death.[32] Although it is possible that high levels of creatinine kinase could build up in the setting of multiorgan failure, it could also be a proxy marker for severe myopathy affecting respiratory function. This could suggest that identification and management of myopathy could play a factor in improving outcomes in critically ill patients.

Despite not acutely associated, there is a third category that has been predominantly recognised in the period after having COVID-19: that of small fibre neuropathy. Two case series demonstrated small fibre neuropathy, proven on either autonomic testing or skin biopsy, in patients who recovered from COVID-19.[33,34] Symptoms included new onset paraesthesia and autonomic dysfunction, and symptom onset occurred several weeks to several months after acute SARS-CoV-2 infection. Despite the plausibility of para-infectious or post-infectious immune dysregulation, a causal relationship between SARS-CoV-2 infection and the development of a small fibre neuropathy has not been established. In a case series, ten of the 17 patients received a form of immunotherapy (corticosteroids or intravenous immunoglobulin), and eight of these had improvement in their symptoms from the nadir.[33] However, all seven patients who were not treated also had improvement in their symptoms.

Isolated autonomic dysfunction is also commonly reported in the cohort with post-COVID-19 syndrome.[35] In the most comprehensive of these studies, 41% of patients had symptoms of orthostatic intolerance without objective evidence of heart rate or blood pressure abnormalities on autonomic (tilt table) testing.[36] This combination is not suggestive of neuropathy-related autonomic dysfunction, but rather overlaps with chronic fatigue and other central sensitisation syndromes (Box).

Seizures

Seizures are uncommon in COVID-19 and are largely driven either by pre-existing CNS pathology (including pre-existing epilepsy) or by new intracranial pathology due to COVID-19. Electroencephalogram (EEG) changes in COVID-19 are most commonly an abnormal background rhythm or diffuse or focal intermittent slowing.[37] The presence of intracranial disease or epileptiform discharges on EEG increase the likelihood of status epilepticus.[38] Interestingly, the risk of long term seizures is predicted by pre-existing epilepsy or by the presence of a structural CNS lesion and not by the severity of SARS-CoV-2 infection, seizures during the acute illness, or EEG abnormalities.[39] This means that long term antiseizure medications are rarely required (Box).

Immune-mediated neurological manifestations of COVID-19

Encephalitis

Autoimmune encephalitis is a rare but significant symptom of COVID-19. Encephalitis is a late manifestation of COVID-19, occurring on average a fortnight after the onset of symptoms, and most commonly presents with altered consciousness and seizures.[40] Imaging changes can be as specific as the typical changes of limbic encephalitis, with mesial temporal lobe T2 FLAIR (T2-weighted-fluid-attenuated inversion recovery) changes on magnetic resonance imaging (MRI), or as broad as T2 lesions in the cortex, white matter or deep grey nuclei.[41]

Cerebrospinal fluid may be normal or, more commonly, show elevated protein.[40] Pleocytosis is less common.

Specific autoimmune encephalitis syndromes have been described after SARS-CoV-2 infection. In one systematic review of autoimmune encephalitis cases in the literature, limbic encephalitis (37%) was most common, followed by N-methyl-D-aspartate receptor (NMDAR) autoimmune encephalitis (26%) and new onset refractory status epilepticus (11%).[42] As with these syndromes outside of COVID-19, encephalitis after COVID-19 generally responds to immunotherapy. Successful treatment regimens have included corticosteroids, intravenous immunoglobulin, plasma exchange, and rituximab.[43] Overall encephalitis after COVID-19 could provide a unique opportunity to examine the pathogenesis of immune-mediated CNS disease, given the likely precipitant (COVID-19) is known.

Guillain–Barré syndrome

GBS is a well documented immune-mediated para-infectious manifestation that had been identified early in the pandemic as a potential complication of COVID-19. Despite being a plausible sequela of COVID-19, there have been opposing views on whether GBS in COVID-19 is in line with the standard prevalence in the non-pandemic era, or whether there is a potential causal effect of COVID-19 in inciting GBS. One of the larger GBS studies reported a drop in the incidence of GBS in the United Kingdom during the pandemic era (2020) compared with the pre-pandemic years (2016–2019), and no relationship between the regional incidence of COVID-19 and GBS.[44] The study authors accept that the restrictions imposed by the pandemic were likely to reduce other pathogen-associated GBS, but still conclude an unlikely causal link between COVID-19 and GBS.

Conversely, two retrospective multicentre Italian studies[45,46] and a multicentre Spanish study[47] evaluated the incidence of GBS in patients with COVID-19 compared with patients without COVID-19 and demonstrated a significant increase in GBS in patients with COVID-19, inferring a potential causal link. However, these studies only covered a short period of time, and the number of patients in these studies was small. Interestingly, there seems to be a specific phenotype of COVID-19-associated GBS. Multiple electrophysiology case series have identified higher rates of demyelinating pathology as opposed to axonal and more common involvement of cranial nerves.[48,49] At this stage, all we can conclude is that GBS is a possible rare complication of SARS-CoV-2 infection and that prospective monitoring of the incidence of GBS along with COVID-19 is warranted (Box).

Complications of endothelial dysfunction and thrombosis in COVID-19

Stroke

Early in the COVID-19 pandemic, there were reports of increased cerebrovascular disease, with a particular concern of ischaemic stroke occurring in young people.[50] Subsequent large multicentre studies have identified the incidence of stroke in COVID-19 ranging from 1% to 2%.[51,52] There are conflicting reports whether strokes in COVID-19 disproportionally affect younger persons,[53,54] as well as whether patients display the traditional vascular risk factors (hypertension, diabetes, atrial fibrillation).[53] It is also unclear whether the rate of stroke in COVID-19 is altered from the baseline population rate. One case–control study evaluating stroke presentations to multiple emergency departments across Spain identified no significant difference in the rate of stroke between patients testing positive for SARS-CoV-2 and those testing negative.[55]

What is clearer is that patients with severe COVID-19 disease (requiring intensive care admission or mechanical ventilation) have an elevated risk of stroke.[51,53] Given people with comorbid conditions, including the aforementioned vascular risk factors, are more likely to develop severe COVID-19, it is possible that this could be explained by common risk factors. Other studies have observed unique characteristics of stroke during SARS-CoV-2 infection. Several multicentre studies have reported large vessel occlusion as being over-represented in COVID-19-associated cerebrovascular disease,[54,56] and, in particular, multivessel large-vessel occlusion.[56,57] In addition, both systemic markers of inflammation (C-reactive protein, erythrocyte sedimentation rate) and markers of clot formation and breakdown (D-dimer) have been associated with stroke in patients with COVID-19.[58,59] There is also a higher prevalence of antiphospholipid antibodies in COVID-19, specifically IgG directed against phosphatidylserine/prothrombin,[60] which could provide a link between the systemic inflammation and the COVID-19-associated coagulopathy.

As previously discussed, endothelial dysfunction and endotheliitis may also have a role in CNS vascular disease during COVID-19. High resolution MRI scans of the vessel wall have demonstrated enhancement and thickening of CNS arteries in patients with COVID-19 and cryptogenic stroke.[61] These vessel wall changes are also seen in patients with COVID-19 presenting only with acute encephalopathy, although in this cohort they did not correlate with ischaemia or other imaging changes of vasculopathy,[62] suggesting they are a product of systemic inflammation but may not lead to cerebrovascular disease. There are few case reports of CNS vasculitis during COVID-19,[63] which is a more typical clinical representation of inflammatory endothelial dysfunction. Overall, the evidence supports cerebrovascular disease in COVID-19 as associated with systemic COVID-19 disease and related coagulopathy rather than as a form of vasculitis.

Other cerebrovascular disorders

Other rarer vascular disorders that have been reported during SARS-CoV-2 infection are cerebral venous sinus thrombosis and posterior reversible encephalopathy syndrome. The incidence of cerebral venous sinus thrombosis in COVID-19 has been estimated at up to 3520 cases per million population per year, well above the reported incidence of five cases per million per year in the general population.[64] Unlike arterial stroke in COVID-19, which has been reported at occurring between ten and 14 days after COVID-19 symptom onset, the onset of cerebral venous sinus thrombosis occurs within the first 24–72 hours of COVID-19. The most common symptom is headache, and, in one study, it had a reported mortality of 25%. Similar to arterial stroke, these patients did not demonstrate the typical thrombosis risk factors.[64]

Posterior reversible encephalopathy syndrome during SARS-CoV-2 infection has been less reported in the literature. A systematic review identified 30 cases of posterior reversible encephalopathy syndrome reported in the literature, with 80% occurring in the setting of severe COVID-19 disease.[65] Clinically, it presents similarly to posterior reversible encephalopathy syndrome due to other causes. A hypertensive episode is present in 75% of cases and altered consciousness is the most common presenting symptom. However, radiologically, there is a significant proportion of patients (50%) who demonstrate

haemorrhage,[65] which is another indication of the coagulopathy seen in COVID-19 (Box).

Neurological symptoms of the post-COVID-19 syndrome

Evidence for neurological involvement and injury

Two large population studies have raised the prospect of SARS-CoV-2 infection predisposing to neurological disease. The first study compared the incidence of neurological disorders at 12 months after the development of acute COVID-19 and identified an elevated risk of developing a broad variety of neurological disorders from migraine to Alzheimer disease.[66] Given the considerable variance in different pathologies and aetiologies of these conditions, it is hard to conceptualise how COVID-19 could affect the risk of such divergent diseases. This is particularly interesting for neurodegenerative diseases with a decades' long pre-clinical prodrome, such as Alzheimer disease, given the follow-up time in this study was only 12 months. It is possible that SARS-CoV-2 infection may be causally related to some inflammatory conditions such as GBS or encephalitis but hasten the diagnosis of previously present but undiagnosed neurodegenerative diseases such as Parkinson or Alzheimer disease. This should become clearer with time and longer follow-up studies. It is also possible the diagnosis of other health conditions will increase after any significant adverse health event, not just SARS-CoV-2 infection.

The other large-scale study was a two-year retrospective cohort study including 1 284 437 propensity score matched patients with COVID-19 versus respiratory matched controls.[67] The authors evaluated the incidence and hazard ratio (six-month and time varying) for a range of neurological conditions over a two-year period. They identified an increased risk of cognitive deficits, dementia, psychotic disorder, and epilepsy or seizures. However, the risk of dementia and cognitive deficits was mainly driven by the older adult population (no significant difference was seen in children or adults) and the Delta variant, which is characterised by more severe COVID-19. This again is suggestive of pre-existing or prodromal illness unmasked by a significant health event.

Cognition dysfunction and other sequelae

Cognitive complaints, including memory impairment and slowed speed of processing, are common neurological symptoms reported in post-COVID-19 syndrome.[68] Studies of cognition in patients after SARS-CoV-2 infection are heterogenous. This is due to the varying definitions of abnormal cognition, the neuropsychological tests used (particularly the use of tests with a low ceiling, such as the Montreal Cognitive Assessment), and the potential confounding effect of fatigue, mood changes, and anxiety on performance in neuropsychological testing. For example, in a study of patients after severe COVID-19, almost half of patients reported cognitive complaints, and just over half of patients reported fatigue, supported objectively by abnormal fatigue scores.[68] Despite composite cognitive scores demonstrating no differences from normative population data, on deeper cognitive analysis there was a slight reduction in day-to-day processing of information and planning that correlated with fatigue, anxiety and mood changes. Although it is difficult to identify any causal relationship in either direction, this does highlight the potential impact that confounders can have on the assessment of cognition.

Other studies have demonstrated similar comorbid symptoms occurring with cognitive dysfunction, with high fatigue scores in up to 85% of patients.[69] There have also been multiple negative studies that did not identify any change in cognitive function in people with post-COVID-19 syndrome and cognitive complaints,[70,71] or in which the reduction in cognition would be considered to be within the variance of a normal population and not clinically significant.[72,73] Studies done with more comprehensive cognitive assessments have identified a subset of patients with post-COVID-19 syndrome who demonstrate objective cognitive changes. A cross-sectional study found that of 740 patients with previous SARS-CoV-2 infection, 18% had slowed processing speed, 16% had executive dysfunction, 15% had issues with phonemic fluency, 24% had memory encoding problems, and 23% had difficulties with memory recall.[74] Patients admitted to hospital, a proxy variable for severe disease, were more likely to have impaired cognition.

Overall, the factors most strongly associated with poor cognitive function in the first six months after SARS-CoV-2 infection are severe disease, intensive care requirement, and hypoxia.[75-77] On longer follow-up, many of these patients have improved cognition at 12 months, albeit still lower than baseline.[74]

In conjunction with cognitive studies, biomarkers of neuronal injury provide an insight into the potential for long term neurological sequelae. Neurofilament light (NfL) is a well validated biomarker of neuroaxonal breakdown[78] which has been used in neurodegenerative conditions, such as Alzheimer disease, and in neuroinflammatory conditions, such as multiple sclerosis.[79] NfL could be used as a fluid biomarker for neuroaxonal injury in acute SARS-CoV-2 infection and to assess for persisting neurodegeneration.

NfL levels in the blood have been demonstrated to be elevated during acute SARS-CoV-2 infection and correlate with severe disease[80-84] but not with mild to moderate disease.[85] NfL levels were similar to those seen during other severe pulmonary infections such as bacterial pneumonia[86] or influenza.[87] Cerebrospinal fluid levels of NfL were higher in patients with central neurological complications of COVID-19 (defined as reduced consciousness or central weakness).[83] Longitudinal studies of NfL and other biomarkers of CNS injury, such as glial fibrillary acidic protein, normalise by six months following severe illness.[88]

The strongest evidence for potential neurodegeneration leading to cognitive dysfunction comes from a study using a pre-existing UK biobank.[89] It demonstrated longitudinal cortical volume loss in limbic brain regions functionally connected to the primary olfactory cortex in 56–62% of patients with COVID-19, and deficits in the neuropsychological tests of processing speed and executive dysfunction. However, cerebral volume losses were small, and there was minimal correlation between cognitive testing and volume loss indicating that these changes may not be clinically or functionally significant (Box).

Future directions and conclusions

Neurological symptoms are common during SARS-CoV-2 infection and reflect a broad spectrum of neurological disorders. An understanding of the clinical characteristics of these complications are important when managing patients with COVID-19.

These complications also provide a unique opportunity to further our knowledge on the pathogenesis of these neurological disorders independent of COVID-19. The efforts to create registries for neurological manifestations of COVID-19 should now be focused on converting these databases to biobanks to further this pursuit.

Commonly reported long term neurological sequelae of COVID-19 are cognitive dysfunction and dysautonomia. However, assessment of cognitive dysfunction in post-COVID-19 syndrome has been confounded by a high prevalence of comorbid fatigue, anxiety, and mood disorders and by heterogenous definitions and methodology. Future studies on long term cognitive dysfunction should be guided by centrally agreed upon research procedures to ensure reliability and reproducibility. Markers of neuroaxonal breakdown, such as NfL, suggest no significant neuronal injury apart from during severe acute COVID-19, which is not unique to COVID-19 but still significant to society given the large number of people potentially affected. The long term impact of COVID-19 on neurological diseases remains uncertain and requires ongoing vigilance through longitudinal studies.

Open access: Open access publishing facilitated by Monash University, as part of the Wiley – Monash University agreement via the Council of Australian University Librarians.

Competing interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed. ■

1 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77: 683-690.

2 Kacem I, Gharbi A, Harizi C, et al. Characteristics, onset, and evolution of neurological symptoms in patients with COVID-19. *Neurol Sci* 2021; 42: 39-46.

3 Travi G, Rossotti R, Merli M, et al. Neurological manifestations in patients hospitalized with COVID-19: a retrospective analysis from a large cohort in Northern Italy. *Eur J Neurosci* 2021; 53: 2912-2922.

4 Rogers JP, Watson CJ, Badenoch J, et al. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. *J Neurol Neurosurg Psychiatry* 2021; 92: 932-941.

5 Teaima AA, Salem OM, Teama MAEM, et al. Patterns and clinical outcomes of olfactory and gustatory disorders in six months: Prospective study of 1031 COVID-19 patients. *Am J Otolaryngol* 2022; 43: 103259.

6 Bauer L, Laksono BM, de Vrij FMS, et al. The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. *Trends Neurosci* 2022; 45: 358-368.

7 Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol* 2020; 11: 573095.

8 Bulfamante G, Bocci T, Falleni M, et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J Neurol* 2021; 268: 4486-4491.

9 Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020; 19: 919-929.

10 Fullard JF, Lee HC, Voloudakis G, et al. Single-nucleus transcriptome analysis of human brain immune response in patients with severe COVID-19. *Genome Med* 2021; 13: 118.

11 Poloni TE, Medici V, Moretti M, et al. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. *Brain Pathol* 2021; 31: e12997.

12 Deigendesch N, Sironi L, Kutza M, et al. Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. *Acta Neuropathol* 2020; 140: 583-586.

13 Menge T, Hemmer B, Nessler S, et al. Acute disseminated encephalomyelitis: an update. *Arch Neurol* 2005; 62: 1673-1680.

14 Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. *Acta Pharmacol Sin* 2023; 44: 695-709.

15 Poudel A, Poudel Y, Adhikari A, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. *PLoS One* 2021; 16: e0256744.

16 Kirschenbaum D, Imbach LL, Rushing EJ, et al. Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19. *Neuropathol Appl Neurobiol* 2021; 47: 454-459.

17 Wierzba-Bobrowicz T, Krajewski P, Tarka S, et al. Neuropathological analysis of the brains of fifty-two patients with COVID-19. *Folia Neuropathol* 2021; 59: 219-231.

18 Frontera JA, Melmed K, Fang T, et al. Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care* 2021; 35: 693-706.

19 López JT, García-Azorín D, Planchuelo-Gómez A, et al. Phenotypic characterization of acute headache attributed to SARS-CoV-2: an ICHD-3 validation study on 106 hospitalized patients. *Cephalalgia* 2020; 40: 1432-1442.

20 Magdy R, Hussein M, Ragaie C, et al. Characteristics of headache attributed to COVID-19 infection and predictors of its frequency and intensity: a cross sectional study. *Cephalalgia* 2020; 40: 1422-1431.

21 Sahin BE, Celikbilek A, Kocak Y, Hizmali L. Patterns of COVID-19-related headache: a cross-sectional study. *Clin Neurol Neurosurg* 2022; 219: 107339.

22 Toptan T, Aktan C, Basari A, Bolay H. Case series of headache characteristics in COVID-19: headache can be an isolated symptom. *Headache* 2020; 60: 1788-1792.

23 García-Azorín D, Layos-Romero A, Porta-Etessam J, et al. Post-COVID-19 persistent headache: a multicentric 9-months follow-up study of 905 patients. *Cephalalgia* 2022; 42: 804-809.

24 Souza DD, Shivde S, Awatare P, et al. Headaches associated with acute SARS-CoV-2 infection: a prospective cross-sectional study. *SAGE Open Med* 2021; 9: 20503121211050227.

25 Trigo J, García-Azorín D, Sierra-Mencía A, et al. Cytokine and interleukin profile in patients with headache and COVID-19: a pilot, CASE-control, study on 104 patients. *J Headache Pain* 2021; 22: 51.

26 Karadaş O, Öztürk B, Sonkaya AR, et al. Latent class cluster analysis identified hidden headache phenotypes in COVID-19: impact of pulmonary infiltration and IL-6. *Neurol Sci* 2021; 42: 1665-1673.

27 Bolay H, Karadas O, Oztürk B, et al. HMGB1, NLRP3, IL-6 and ACE2 levels are elevated in COVID-19 with headache: a window to the infection-related headache mechanism. *J Headache Pain* 2021; 22: 94.

28 Han CY, Tarr AM, Gewirtz AN, et al. Brachial plexopathy as a complication of COVID-19. *BMJ Case Rep* 2021; 14: e237459.

29 Nanda S, Handa R, Anand R, et al. Curious case of steroid responsive diffuse anterior horn cell disease associated with COVID-19 infection. *Neurol Sci* 2021; 42: 3415-3417.

30 Cabañes-Martínez L, Villadóniga M, González-Rodríguez L, et al. Neuromuscular involvement in COVID-19 critically ill patients. *Clin Neurophysiol* 2020; 131: 2809-2816.

31 Bocci T, Campiglio L, Zardoni M, et al. Critical illness neuropathy in severe COVID-19: a case series. *Neurol Sci* 2021; 42: 4893-4898.

32 De Rosa A, Verrengia EP, Merlo I, et al. Muscle manifestations and CK levels in COVID infection: results of a large cohort of patients inside a Pandemic COVID-19 Area. *Acta Myol* 2021; 40: 1-7.

33 Oaklander AL, Mills AJ, Kelley M, et al. Peripheral neuropathy evaluations of patients with prolonged long COVID. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e1146.

34 Abrams RMC, Simpson DM, Navis A, et al. Small fiber neuropathy associated with SARS-CoV-2 infection. *Muscle Nerve* 2022; 65: 440-443.

35 Buoite Stella A, Furlanis G, Frezza NA, et al. Autonomic dysfunction in post-COVID patients with and without neurological symptoms: a prospective multidomain observational study. *J Neurol* 2022; 269: 587-596.

36 Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res* 2021; 31: 385-394.

37 Danoun OA, Zillgitt A, Hill C, et al. Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19. *Epilepsy Behav* 2021; 118: 107923.

38 Lin L, Al-Faraj A, Ayub N, et al. Electroencephalographic abnormalities are common in COVID-19 and are associated with outcomes. *Ann Neurol* 2021; 89: 872-883.

39 Asadi-Pooya AA, Kouhanjani MF, Nemati H, et al. A follow-up study of patients with COVID-19 presenting with seizures. *Epilepsy Behav* 2021; 122: 108207.

40 Siow I, Lee KS, Zhang JJY, et al. Encephalitis as a neurological complication of COVID-19:

A systematic review and meta-analysis of incidence, outcomes, and predictors. *Eur J Neurol* 2021; 28: 3491-3502.

41 Islam MA, Cavestro C, Alam SS, et al. Encephalitis in patients with COVID-19: a systematic evidence-based analysis. *Cells* 2022; 11: 2575.

42 Nabizadeh F, Balabandian M, Sodeifian F, et al. Autoimmune encephalitis associated with COVID-19: a systematic review. *Mult Scler Relat Disord* 2022; 62: 103795.

43 Cao A, Rohaut B, Le Guennec L, et al. Severe COVID-19-related encephalitis can respond to immunotherapy. *Brain* 2020; 143: e102.

44 Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain–Barré syndrome. *Brain* 2021; 144: 682-693.

45 Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain–Barré syndrome and COVID-19: a 1-year observational multicenter study. *Eur J Neurol* 2022; 29: 3358-3367.

46 Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain–Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry* 2021; 92: 751-756.

47 Fragiel M, Miró O, Llorens P, et al. Incidence, clinical, risk factors and outcomes of Guillain–Barré in COVID-19. *Ann Neurol* 2021; 89: 598-603.

48 Luijten LWG, Leonhard SE, van der Eijk AA, et al. Guillain–Barré syndrome after SARS-CoV-2 infection in an international prospective cohort study. *Brain* 2021; 144: 3392-3404.

49 Foresti C, Servalli MC, Frigeni B, et al. COVID-19 provoking Guillain–Barré syndrome: the Bergamo case series. *Eur J Neurol* 2021; 28: e84-e85.

50 Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. *N Engl J Med* 2020; 382: e60.

51 Sluis WM, Linschoten M, Buijs JE, et al. Risk, clinical course, and outcome of ischemic stroke in patients hospitalized with COVID-19: a multicenter cohort study. *Stroke* 2021; 52: 3978-3986.

52 Khandelwal P, Al-Mufti F, Tiwari A, et al. Incidence, characteristics and outcomes of large vessel stroke in COVID-19 cohort: an international multicenter study. *Neurosurgery* 2021; 89: E35-E41.

53 Shakil SS, Emmons-Bell S, Rutan C, et al. Stroke among patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. *Stroke* 2022; 53: 800-807.

54 Shahjouei S, Tsivgoulis G, Farahmand G, et al. SARS-CoV-2 and stroke characteristics: a report from the Multinational COVID-19 Stroke Study Group. *Stroke* 2021; 52: e117-e130.

55 García-Lamberechts EJ, Miró O, Fragiel M, et al. A case–control analysis of stroke in COVID-19 patients: results of unusual manifestations of COVID-19-study 11. *Acad Emerg Med* 2021; 28: 1236-1250.

56 John S, Kesav P, Mifsud VA, et al. Characteristics of large-vessel occlusion associated with COVID-19 and ischemic stroke. *AJNR Am J Neuroradiol* 2020; 41: 2263-2268.

57 Perry RJ, Smith CJ, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry* 2021; 92: 242-248.

58 Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020; 5: 279-284.

59 Goyal N, Sodani AK, Jain R, Ram H. Do elevated levels of inflammatory biomarkers predict the risk of occurrence of ischemic stroke in SARS-CoV2?: an observational study. *J Stroke Cerebrovasc Dis* 2021; 30: 106063.

60 Benjamin LA, Paterson RW, Moll R, et al. Antiphospholipid antibodies and neurological manifestations in acute COVID-19: a single-centre cross-sectional study. *EClinicalMedicine* 2021; 39: 101070.

61 Mazzacane F, Zito A, Magno S, et al. Vessel wall magnetic resonance imaging in COVID-19-associated cryptogenic ischemic stroke. *Eur J Neurol* 2022; 29: 615-619.

62 Uginet M, Breville G, Hofmeister J, et al. Cerebrovascular complications and vessel wall imaging in COVID-19 encephalopathy-a pilot study. *Clin Neuroradiol* 2022; 32: 287-293.

63 Timmons GM, Rempe T, Bevins EA, et al. CNS lymphocytic vasculitis in a young woman with COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e1048.

64 Al-Mufti F, Amuluru K, Sahni R, et al. Cerebral venous thrombosis in COVID-19: a New York metropolitan cohort study. *AJNR Am J Neuroradiol* 2021; 42: 1196-1200.

65 Yeahia R, Schefflein J, Chiarolanzio P, et al. Brain MRI findings in COVID-19 patients with PRES: a systematic review. *Clin Imaging* 2022; 81: 107-113.

66 Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022; 28: 2406-2415.

67 Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry* 2022; 9: 815-827.

68 Holdsworth DA, Chamley R, Barker-Davies R, et al. Comprehensive clinical assessment identifies specific neurocognitive deficits in working-age patients with long-COVID. *PLoS One* 2022; 17: e0267392.

69 Krishnan K, Miller AK, Reiter K, Bonner-Jackson A. Neurocognitive profiles in patients with persisting cognitive symptoms associated with COVID-19. *Arch Clin Neuropsychol* 2022; 37: 729-737.

70 Dressing A, Bormann T, Blazhenets G, et al. Neuropsychologic profiles and cerebral glucose metabolism in neurocognitive long COVID syndrome. *J Nucl Med* 2022; 63: 1058-1063.

71 Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers". *Ann Clin Transl Neurol* 2021; 8: 1073-1085.

72 Apple AC, Oddi A, Peluso MJ, et al. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. *Ann Clin Transl Neurol* 2022; 9: 221-226.

73 Andriuta D, Si-Ahmed C, Roussel M, et al. Clinical and imaging determinants of neurocognitive disorders in post-acute COVID-19 patients with cognitive complaints. *J Alzheimers Dis* 2022; 87: 1239-1250.

74 Becker JH, Lin JJ, Doernberg M, et al. Assessment of cognitive function in patients after COVID-19 infection. *JAMA Netw Open* 2021; 4: e2130645.

75 Nersesjan V, Fonsmark L, Christensen RHB, et al. Neuropsychiatric and cognitive outcomes in patients 6 months after COVID-19 requiring hospitalization compared with matched control patients hospitalized for non-COVID-19 illness. *JAMA Psychiatry* 2022; 79: 486-497.

76 Ferrucci R, Dini M, Rosci C, et al. One-year cognitive follow-up of COVID-19 hospitalized patients. *Eur J Neurol* 2022; 29: 2006-2014.

77 Liu YH, Chen Y, Wang QH, et al. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. *JAMA Neurol* 2022; 79: 509-517.

78 Khalil M, Pirpamer L, Hofer E, et al. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. *Nat Commun* 2020; 11: 812.

79 Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol* 2018; 14: 577-589.

80 Prudencio M, Erben Y, Marquez CP, et al. Serum neurofilament light protein correlates with unfavorable clinical outcomes in hospitalized patients with COVID-19. *Sci Transl Med* 2021; 13: eabi7643.

81 Verde F, Milone I, Bulgarelli I, et al. Serum neurofilament light chain levels in Covid-19 patients without major neurological manifestations. *J Neurol* 2022; 269: 5691-5701.

82 De Lorenzo R, Lore NI, Finardi A, et al. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. *J Neurol* 2021; 268: 4436-4442.

83 Virhammar J, Naas A, Fallmar D, et al. Biomarkers for central nervous system injury in cerebrospinal fluid are elevated in COVID-19 and associated with neurological symptoms and disease severity. *Eur J Neurol* 2021; 28: 3324-3331.

84 Kanberg N, Ashton NJ, Andersson LM, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology* 2020; 95: e1754-e1759.

85 Frontera JA, Boutajangout A, Masurkar AV, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement* 2022; 18: 899-910.

86 Chung HY, Neu C, Wickel J, et al. Neurofilament light chain in patients with COVID-19 and bacterial pneumonia. *Ann Neurol* 2021; 90: 174-175.

87 Needham EJ, Ren AL, Digby RJ, et al. Brain injury in COVID-19 is associated with dysregulated innate and adaptive immune responses. *Brain* 2022; 145: 4097-4107.

88 Kanberg N, Simren J, Eden A, et al. Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine* 2021; 70: 103512.

89 Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022; 604: 697-707. ■

Supporting Information

Additional Supporting Information is included with the online version of this article.